PREFRONTAL CONTROL OF THE TACTILE SENSE

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ACADEMIC DISSERTATION

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"*...the creations of our mind shall be a blessing and not a curse to mankind. Never forget this in the midst of your diagrams and equations*"

-Albert Einstein, speech to students in California Institute of Technology (The New York Times, 1931)

Dedicated to the memory of my mother, Tarja

Abstract

Sense of touch provides information about textures, objects and physical forces acting on our body. Tactile information also guides the motor system by providing feedback of our internally generated movements. The aim of this thesis was to dissect the neural mechanisms underlying different levels of tactile processing in healthy subjects. In the first study of the thesis, the influence of temporal properties of stimulation on tactile spatial discrimination ability was studied. The study revealed that the ability to discriminate adjacent tactile stimuli as spatially distinct was influenced by temporal features of stimulation.

The prefrontal cortex, a brain area involved in many complex cognitive abilities such as working memory, attention and introspection, has been suggested to modulate the functions of primary cortical areas such as the primary somatosensory cortex. However, in the prefrontal areas, there is considerable interindividual variability in the topography of neural structure and function that provides a challenge to studies addressing control of primary sensory areas by the prefrontal cortex. In the second study of the thesis, the challenge of interindividual variability was addressed by determining the individual neural pathways between the primary somatosensory cortex and the prefrontal cortex. First, the somatosensory representation area of the right hand thenar skin was functionally determined by blocking the sensation with navigated transcranial magnetic stimulation. The somatosensory cortical site in which the magnetic stimulation blocked the tactile stimuli, served as a seed point for the probabilistic tractography between the primary somatosensory cortex and two prefrontal areas of interest: the middle frontal gyrus and the superior frontal gyrus. These two tractography-informed prefrontal areas were probed with transcranial magnetic stimulation pulses which were delivered during a tactile temporal discrimination task. The results showed that the transcranial magnetic stimulation of the middle frontal gyrus, but not that of the superior frontal gyrus, reduced the temporal discrimination ability when compared to sham stimulation. Moreover, this impairment effect was temporally and spatially specific: the effect was dependent on the transcranial magnetic stimulation delay and the location of tactile test stimuli. In conclusion, the second study of the thesis suggested that the prefrontal cortex contains neural substrates for fine control of tactile discrimination.

Metacognition, “knowing about knowing”, refers to the ability of humans to monitor and control one’s own cognitive processes. Lesion and brain imaging studies suggest that the prefrontal cortex is important for metacognition, but there are only few transcranial magnetic stimulation studies using state-of-art, bias-free measures of metacognitive ability. In the third study of the thesis, the metacognitive accuracy of tactile working memory was explored with a similar kind of tractography-based transcranial magnetic stimulation approach as in the second study. Two distinct prefrontal areas, the middle frontal gyrus and the superior frontal gyrus, were stimulated while the subjects performed tactile spatial and temporal working memory tasks. Subjective evaluations of confidence were used to calculate the metacognitive accuracy in each stimulation site and working memory task condition. The results showed that transcranial magnetic stimulation of the superior frontal gyrus, but not that of the middle frontal gyrus, enhanced the metacognitive accuracy of the temporal working memory task. When the superior frontal gyrus was stimulated, the subjects were able to better match the incorrectly performed test trials with lower confidence. In the spatial working memory task in which the tactile stimuli were identical to the temporal working memory task, the stimulation of either the middle frontal or superior frontal gyrus had no effect on the metacognitive accuracy. The results of the third study indicate that the prefrontal cortex might contain specific structural correlates for the metacognitive ability.

Contents

List of original publications

This thesis is based on the following publications:

I Boldt R*, **Gogulski J***, Guzmán-Lopez J, Carlson S, Pertovaara A. Two-point tactile discrimination ability is influenced by temporal features of stimulation. Experimental Brain Research. 2014; 232(7):2179-2185.

II **Gogulski J***, Boldt R*, Savolainen P, Guzmán-Lopez J, Carlson S, Pertovaara A. A segregated neural pathway for prefrontal top-down control of tactile discrimination. Cerebral Cortex. 2015; 25(1):161-166.

III **Gogulski J***, Zetter R*, Nyrhinen M, Pertovaara A, Carlson S. Neural substrate for metacognitive accuracy of tactile working memory. Cerebral Cortex. 2017; 27(11):5343-5352.

*Shared first authorship

The publications are referred to in the text by their roman numerals. Study I has been used in another doctoral thesis ("Functional and anatomical brain networks" by Robert Boldt).

Author contributions

I contributed to the design, measurements, data analysis, writing the manuscripts and interpretation of the results in all the studies (I-III).

Abbreviations

AUC	Area under the curve
BA	Brodmann area
CI	Confidence interval
cTBS	Continuous theta-burst stimulation
DWI	Diffusion-weighted imaging
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EMG	Electromyography
EPI	Echo-planar imaging
fMRI	Functional magnetic resonance imaging
FOV	Field-of-view
ISI	Interstimulus interval
MEG	Magnetoencephalography
MFG	Middle frontal gyrus
MRI	Magnetic resonance imaging
PFC	Prefrontal cortex
rMT	Resting motor threshold
ROC	Relative operating characteristic
S1	Primary somatosensory cortex
SDT	Signal detection theory
SFG	Superior frontal gyrus
TE	Echo time
TR	Repetition time
TMS	Transcranial magnetic stimulation
WM	Working memory

1. Introduction

The environment we live in provides us an enormous amount of information every moment. We see, smell, hear and touch our surroundings, and it is usually easy for us to distinguish relevant from irrelevant sensory information. The brain manages to deal with all this information in an incredibly flexible and efficient way so that it feels almost automatic. However, if the brain is not healthy, these abilities become aberrant. For example, a person suffering from schizophrenia may have difficulties in distinguishing the sources, meanings and relations of sensory stimuli. In this thesis, I will investigate how sensory information is processed in the brain of healthy subjects and how different aspects of stimulation are being distinguished. I will focus on the tactile sense, and use contemporary brain imaging, brain stimulation and behavioral measurement techniques to dissect the neurobiological bases of these processes. A main brain area of interest will be the prefrontal cortex (PFC), which has been associated with higher cognitive functions such as attention, short-term memory and executive functions (Fuster, 2001). The PFC is one of the evolutionary youngest brain areas and it is particularly highly developed in humans. A challenging feature of the PFC is the large interindividual variability in the functional anatomy. Therefore, pin-pointing fine cognitive functions in the PFC may sometimes require customized research protocols.

To be able to study tactile processing in a deeper way, one needs to first investigate how the somatosensory system processes different kinds of stimuli. The first study of the thesis investigated whether the ability to discriminate two pulses as spatially separate varies with interstimulus interval (ISI) of the test stimulus pair. Additionally, it was tested whether the length of the test pulse train influences the two-point discrimination ability. The aim was to find out, how the temporal features of stimulation affect the two-point discrimination ability.

One of the challenges for modern neuroscience is, how to take into account the variability between individuals. Despite the general macroanatomical similarities, every brain is unique. Therefore, the use of normalization and group-level analyses may sometimes mask otherwise evident findings. In study II, the attempt was to overcome these challenges by taking into account the interindividual anatomical differences in brain anatomy. Neural tracts between the primary somatosensory cortex (S1) and the PFC were determined with diffusion-weighted imaging (DWI) and tractography. Two end points of the tracts in the PFC, the middle frontal gyrus (MFG) and the superior frontal gyrus (SFG), were probed with navigated transcranial magnetic stimulation (TMS) during tactile temporal discrimination tasks. Additionally, two different locations of skin stimulation were tested.

To be able to use the perceived information to guide further action, short-term storage and manipulation of the information is important. This kind of cognitive function is called working memory (WM). Also, to be able to properly learn and adjust for new environmental changes, subjective evaluation of one's own decisions is critical. The ability of humans to introspectively evaluate the success of one's own decisions is called metacognition. In the third study of the thesis, the neuronal basis of metacognitive accuracy was investigated with a similar kind of tractography-based TMS approach as in study II. The subjects performed tactile temporal and spatial WM tasks, during which they received TMS pulses to either the MFG, the SFG or a control stimulation site. Subjective evaluations of confidence were used to calculate the metacognitive accuracy associated with each stimulus condition.

2. Literature review

2.1. The somatosensory system

2.1.1. Anatomy and physiology of the somatosensory system

Daily life requires accurate and fine-tuned sense of touch. For example, successful execution of motor tasks such as grasping and moving objects is dependent on tactile information that interacts with the motor system in a complex fashion (Johansson and Flanagan, 2009).

Tactile sensations are processed in the somatosensory system, which can be anatomically divided into a peripheral and a central part. The peripheral part consists of several types of tactile afferent neurons, all of which carry information about specific features of somatosensory stimuli (Abraira and Ginty, 2013; Johansson and Flanagan, 2009). In glabrous skin, four types of afferents respond to innocuous touch: fast-adapting type I (FA-I), slowly-adapting type I (SA-I), fast-adapting type II (FA-II) and slowly-adapting type II (SA-II). FA-I afferents that are attached to Meissner corpuscles are sensitive to high frequency skin deformation. FA-I afferents have a small receptive field and the highest density in the fingertips. SA-I afferents that are connected with Merkel cells respond to low frequency skin deformations and are also highly represented in the fingertips. FA-II afferents receive information from Pacinian corpuscles and have a much larger receptive field than FA-I and SA-I afferents. FA-II afferents are sensitive to mechanical transients and fast vibrations that propagate through the tissues of the skin. Last, SA-II afferents that are associated with Ruffini endings, respond to skin stretching. In hairy skin, both FA-I and SA-I afferents respond to innocuous tactile stimuli. In both glabrous and hairy skin, free nerve endings that innervate the epidermis encode noxious stimuli.

After activation of mechanoreceptive nerve endings, the signals are transmitted to the brain by action potentials of the sensory nerve fibers. The soma of the first somatosensory nerve cell is located in the dorsal root ganglion, laterally to the spinal cord. Tactile information is passed on further via the ascending dorsal column, lesions of which have shown to abolish fine control of movement (Leonard et al., 1992). The first synapse lies in the dorsal column nuclei (cuneate or gracilis nuclei, depending on the skin area) in the medulla, after which the second axon of the tract decussates. The second synapse of the tract is located in the contralateral thalamus, in the ventral posterior nuclear complex. The thalamic neurons project to the S1, after which the tactile information spreads to the secondary somatosensory cortex and other cortical areas. The S1 comprises Brodmann areas (BA) 1, 2, 3a and 3b, all of which have distinct functions. Afferent input from somatosensory stimulation is first transmitted to area 3b (Kaas, 1983). Area 3a receives information from afferent muscle nerves and has projections to the primary motor cortex (Zarzecki et al., 1978). Therefore, area 3a has been proposed to be important for the control of motor activity. Area 1 is located on the apex of the postcentral gyrus, whereas area 2 is on the posterior wall of postcentral gyrus. Areas 3a and 3b are located anterior to area 1. The location of all three areas has been shown to vary between subjects (Geyer et al., 1999; Grefkes et al., 2001).

2.1.2. Tactile temporal and spatial discrimination

Temporal discrimination refers to the capacity to perceive two temporally separate stimuli as different. In the somatosensory system, it has been shown that with an interstimulus interval (ISI) of approximately 100 ms two electrotactile stimuli are reliably perceived as separate (Pastor et al., 2004). Temporal resolution is much lower in the tactile compared to the auditory system (Gescheider, 1967). Both single-pulse (Hannula et al., 2008) and repetitive TMS (Rocchi et al., 2016) of the S1 have been shown to reduce the tactile temporal discrimination ability. Other ways to study tactile temporal processing include temporal order judgments and simultaneity judgments. The somatotopic location

(Kuroki et al., 2010) of the tactile stimulation as well as posture of the stimulated limb have been shown to affect tactile temporal order judgments (Yamamoto and Kitazawa, 2001).

Spatial discrimination refers to the ability of perceiving two adjacent stimuli as spatially distinct. Perhaps the most common way of assessing spatial resolution of tactile sensations is the assessment of the two-point discrimination threshold. Two-point discrimination ability varies between skin areas, highest acuity being in the glabrous skin (Mancini et al., 2014). Although having been criticized (Craig and Johnson, 2000), the two-point discrimination task has clinical relevance: it has been shown to predict the recovery of upper limb dexterity in stroke patients (Meyer et al., 2014). Spatial discrimination ability can also be determined with e.g. grating orientation (Bleyenheuft and Thonnard, 2007), letter recognition, gap detection (Johnson and Phillips, 1981) or two-point orientation discrimination (Tong et al., 2013) paradigms.

2.2. Working memory

WM refers to short-term storage of information and manipulation of that information to guide behavior (Baddeley, 1992). WM is needed for performing common tasks of everyday life. For example, when tossing coffee into the filter one has to keep in mind the amount that has already been added. WM has been studied massively (4.93 million results in Google Scholar with the search query "working memory") but most of the studies have utilized visual or auditory, rather than tactile tasks. The fronto-parietal network has been shown to be involved in many kinds of WM tasks, including visual, auditory and tactile WM tasks (Rottschy et al., 2012).

The functional organization of WM is still under debate. Electrophysiological recordings in the cortex of non-human primates have shown that single neurons in the PFC are activated during the WM maintenance period in visual (Funahashi et al., 1989), in visual / auditory (Artchakov et al., 2007) and auditory-tactile WM tasks (Vergara et al., 2016). Similar cross-modal coding of information at single cell level in the PFC was also shown when visual-haptic and haptic-haptic WM tasks were used (Wang et al., 2015). Persistent neuronal activity in the PFC has been suggested to form the neuronal basis for WM maintenance (Zylberberg and Strowbridge, 2017; Goldman-Rakic, 1995), but this concept has also been criticized (Curtis and Lee, 2010). A recent study in which functional magnetic resonance imaging (fMRI) -guided TMS reactivated the unattended WM items (Rose et al., 2016), supported the theory according to which short-term synaptic plasticity, rather than spiking activity would account for WM maintenance (Mongillo et al., 2008).

Human fMRI studies have elucidated the role of the PFC in tactile WM processing. Preuschhof et al. (2006) showed that a longer maintenance period (4100 ms) in a vibrotactile WM task was associated with more anterior fMRI activations in the lateral PFC when compared to a shorter WM maintenance period (100 ms). When contrasted with no-memory trials, the WM trials produced activations in the left inferior frontal gyrus, the left inferior parietal lobule and the medial frontal gyrus. A study by Kostopoulos et al. (2007) stated that the midventrolateral PFC (BA47/12 and BA45) is involved in active retrieval of vibrotactile WM information. Recently, by using multivariate pattern analysis techniques on fMRI data, Schmidt et al. (2017) showed that the bilateral premotor cortex, the supplementary motor/cingulate cortex and the right inferior frontal cortex were involved in vibrotactile WM maintenance. Spitzer et al. (2014) showed that functional coupling between the right inferior frontal gyrus and the S1 occurs during WM maintenance of tactile information. Moreover, in their study, mental manipulation of tactile WM contents was parametrically processed in the right inferior frontal cortex. In addition to fMRI studies, WM has also been investigated with electroencephalography (EEG) and magnetoencephalography (MEG) (Roux and Uhlhaas, 2014).

TMS has also been utilized in a couple of tactile WM studies. Auksztulewicz et al. (2011) studied the involvement of the inferior frontal gyrus in tactile WM processing with fMRI-guided, repetitive TMS, and by using a similar WM task as in the study by Spitzer et al. (2014). Pooling the trials of both left and right inferior frontal gyrus stimulation resulted in a significant impairment of performance in the WM manipulation task. In a study by Harris et al. (2002), single-pulse, non-navigated TMS of the contralateral S1 that was applied 300 ms after the start of WM maintenance period reduced the WM performance when compared to the ipsilateral TMS condition. In line with their study, navigated single-pulse TMS of the contralateral S1 during the WM maintenance was shown to impair the tactile WM performance (Ku et al., 2015b). In an earlier study, tractography-guided, single-pulse TMS of the MFG reduced the relative latency in a tactile temporal WM task (Hannula et al., 2010). On the other hand, navigated TMS of the left MFG has also been suggested to impair the performance of vibrotactile WM (Zhao et al., 2017). In conclusion, knowledge of neurobiological frameworks underlying tactile WM is not yet comprehensive.

2.3. Metacognition

An old Buddhist saying goes, "an eye cannot see itself". Nevertheless, humans are capable to introspectively monitor and control their own cognitive processes. This ability is called metacognition, which generally speaking refers to cognition about cognition. Many neuropsychiatric disorders, for example schizophrenia, Alzheimer's disease and traumatic brain injury, involve failures in metacognitive ability (David et al., 2012). The neural underpinnings of metacognition are not well known. Confound-free, quantitative measures of metacognition have been developed only in the last few years (Maniscalco and Lau, 2012). Recently, it has been discussed whether metacognition is a general cognitive capacity (Faivre et al., 2017) or whether metacognition of different cognitive domains (for example perception and memory) is differentiated across distinct neural substrates (Fitzgerald et al., 2017; Fleming et al., 2014).

Lesion and neuroimaging studies have shed some light on the neural bases of metacognitive ability. In general, the PFC seems to be crucial for metacognitive performance (Fleming and Dolan, 2012). Using resting state fMRI and functional connectivity analyses, Baird et al. (2013) showed that the metacognitive performance for visual perception and word recognition memory correlated with different functional networks. Moreover, metacognitive accuracy of visual perception correlated with increased diffusion anisotropy of the right anterior cingulate cortex, whereas metacognitive performance of word recognition memory correlated with increased diffusion anisotropy of the right inferior parietal lobule (Baird et al., 2015). The white-matter microstructure of the anterior corpus callosum and gray matter volume of the anterior PFC have also been shown to correlate with metacognitive performance in a visual perception task (Fleming et al., 2010; McCurdy et al., 2013).

So far, there are only a few TMS studies using the meta-*d'* metric for evaluation of metacognitive performance. In the study by Rounis et al. (2010), the authors demonstrated that bilateral, continuous theta-burst stimulation (cTBS) of the PFC reduced the metacognitive sensitivity in a visual perception task. However, Bor et al. (2017) failed to replicate the results of Rounis et al. (2010). The authors suggest several explanations for the negative results: strict criteria for excluding subjects with unstable behavioral data, a different control TMS site (no cortical control site versus vertex control site) and different ways of measuring the motor threshold (MT). In a study by Fleming et al. (2015), single-pulse, non-navigated TMS of the premotor cortex reduced the metacognitive performance in the incongruent trials of visual discrimination tasks. In an elegant study by Rahnev et al. (2016), fMRI-guided cTBS of the right anterior PFC enhanced the metacognitive performance in a visuospatial perception task.

2.4. The prefrontal cortex

The PFC can be defined as the associative cortex of the frontal lobe (Fuster, 2001). Histologically, three major subdivisions of the PFC can be distinguished: the lateral PFC, the medial frontal cortex and the orbitofrontal cortex (Fig. 1; Ridderinkhof et al., 2004). The lateral PFC can be further divided into the dorsolateral (BA9/46, BA46 and BA8a), the ventrolateral PFC (BA44 and BA45) and the inferior frontal junction (the junction of BA8a, BA6 and BA44). The medial frontal cortex consists of the supplementary motor area, the pre-supplementary motor area (medial BA6), the frontal eye field (BA8) and the dorsomedial PFC (BA9). The orbitofrontal cortex is determined by the medial (BA14), ventral (BA11 and BA13) and lateral (BA12/47) parts, and the frontopolar cortex (BA10), which is the most anterior part of the PFC. In general, the PFC has been shown to be crucial e.g. for executive functions, attention and memory (Miller and Cohen, 2001). Dysfunction of the PFC may lead to neuropsychiatric disorders; e.g., it has been shown that schizophrenia and depression patients have abnormal activation of the PFC (Fitzgerald et al., 2008; Esslinger et al., 2009; Meyer-Lindenberg et al., 2005).

The PFC is anatomically connected with various posterior parts of the brain, as shown by tractography studies (Rojkova et al., 2016). Moreover, the left and right PFC are connected via the frontal commissure, and there are many local short range connections within the frontal cortex (Catani et al., 2012). The PFC is one of the evolutionary youngest brain regions which has been suggested to account for the high interindividual variability in the functional connectivity of the PFC (Mueller et al., 2013).

The role of the PFC in selective attention has been explicated by several influential theories; for example, PFC-induced suppression of distractive or irrelevant sensory information, and PFC-induced facilitation of cortical responses when behaviorally relevant stimuli are present. Empirical basis for the suppression-of-distractors theory has evolved from studies comparing sensory evoked responses recorded from PFC-lesion patients and healthy controls (Yamaguchi and Knight, 1990; Chao and Knight, 1995). On the other hand, a study using concurrent TMS-fMRI supported the facilitation hypothesis (Feredoes et al., 2011). These two prefrontal control mechanisms, the suppression of irrelevant information and the facilitation of relevant information, have also been proposed to work in conjunction with each other (Zanto et al., 2011; Seidl et al., 2012; Gazzaley et al., 2005).

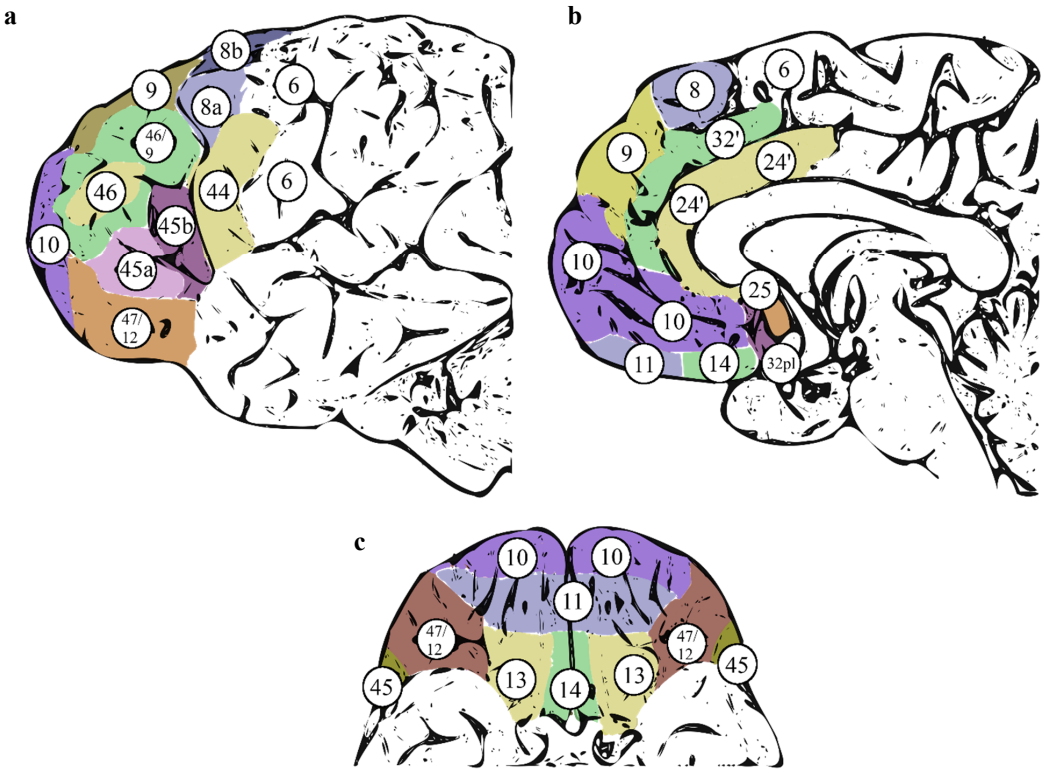

Figure 1: Schematical presentation of the cytoarchitectonic areas of the prefrontal cortex (PFC). Lateral (**a**) and midsagittal (**b**) views of the PFC. (**c**) View from below. The numbers and colored areas refer to Brodmann areas. Adapted and modified from Ridderinkhof et al. 2004.

2.5. Transcranial magnetic stimulation

TMS is a non-invasive brain stimulation technique which enables investigating causal relations between the stimulated brain area and the studied cognitive function. TMS has also been widely used in studies of motor functions (e.g., Ziemann et al., 2008; Tarkka and Stokic, 2013). First modern demonstrations of using TMS for human subjects were shown by Anthony Barker and colleagues in the middle of 1980's (Barker et al., 1985). In the early days of TMS, targeting of the magnetic pulses was based on external landmarks of the skull. Development of MRI-based, real-time navigation of the TMS coil in the early 2000's improved significantly the spatial accuracy of TMS (Ruohonen and Karhu, 2010).

The mechanism of TMS is based on Faraday's law of induction, according to which a change in the magnetic field induces an electric field. A brief electric current in the TMS coil induces a brief (~ 0.1 ms) and strong (up to ~2 T) magnetic field perpendicularly to the electric current. The magnetic field produces an electric field inside the skull perpendicularly to the magnetic field, so the induced electric field is oriented tangentially in relation to the surface of the skull. The overall shape of the induced electric field depends on the coil shape; a circular coil produces a large, round electric field whereas a figure-of-eight coil yields a more focal stimulation (Cohen et al., 1990). Higher stimulation intensity increases the penetration depth of the induced electric field, but it also reduces the focality of the stimulation effect. Measuring the excitability of the M1 cortex (the resting motor threshold, rMT) is the most commonly used way of determining TMS intensity because there is an objective readout (electromyography, EMG) of the effect produced by TMS (Rossi et al., 2009). Other possible ways of determining the intensity are: phosphene threshold (inducing phosphenes via stimulation of the visual cortex; Marg and Rudiak, 1994), estimation of the maximal induced electric field (Ferrarelli et al., 2012), coil-to-cortex distance and active MT (stimulating the M1 while the subject is contracting the corresponding muscle; Hartwigsen et al., 2013).

One of the major reasons to use navigation in TMS studies is the inter-subject variability in brain anatomy. Importantly, the distance between the TMS coil and brain tissue (McConnell et al., 2001), and target site anatomy (Janssen et al., 2014) affect the strength of the induced electric field and thus, the biological effects of TMS. Additionally, different coil orientations stimulate different axonal bundles as shown by tractography-based simulation studies (Nummenmaa et al., 2014). Thus, navigating the coil accurately in relation to the gyri is essential for optimizing the effects of TMS.

In comparison to other widely used non-invasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS) or transcranial alternating current stimulation (tACS), TMS with a figure-of-eight coil produces the most focal stimulation (Woods et al., 2016). Another clinically used brain stimulation technique is electroconvulsive therapy (ECT) in which seizures are induced with an electric current that is passed through the brain. In treatment of major depression, ECT has been suggested to be more efficient than rTMS (Ren et al., 2014).

TMS has proved to be safe for patients and for healthy people. However, the safety guidelines have to be carefully followed when planning an experiment, and a structured safety-screening needs to be gone through always before a TMS experiment (Rossi et al., 2011). In the literature, there are very few case reports about TMS-induced epileptic seizures, most of which have occurred in medicated patients (Rossi et al., 2009). Perhaps the most common discomfort of TMS results from the transient clicking noise induced by the discharging TMS coil. The peak sound-pressure level of this acoustic artifact has been shown to depend mostly on the stimulation intensity, and the auditory spectrum of the artifact has been shown to vary with the coil shape (circular or figure-of-eight coil; Pascual-Leone et al., 1992). Other possible adverse effects of TMS include transient headache, neck pain, syncope, paresthesia, local pain from stimulated muscles and transient hearing changes.

TMS has been reported to have therapeutic applications (Lefaucheur et al., 2014; George et al., 1999). Repetitive TMS applied to the left PFC has proved to be efficient in the treatment of major depression (Perera et al., 2016). Chronic pain has been successfully treated with repetitive TMS of an M1 site contralateral to the pain site (Lefaucheur et al., 2014). The combination of TMS and EEG has a remarkable potential in diagnostics of consciousness disorders such as vegetative state and minimally conscious state (Casarotto et al., 2016). Navigated TMS has also shown to be as accurate as direct cortical stimulation in the presurgical motor mapping of brain tumor patients (Picht et al., 2011; Krieg et al., 2017).

2.6. Diffusion-weighted magnetic resonance imaging and tractography

Brownian motion means that when in a liquid form, water molecules move randomly due to collision of the molecules. If the compartment of these molecules is limited, it results in diffusion in a certain direction. In the brain, when the axons limit the free movement of water molecules, the diffusion is said to be anisotropic. Instead, if water molecules can move freely to all directions, the diffusion is called isotropic. Diffusion-weighted imaging (DWI) can utilize these differences (Mori and Barker, 1999); each voxel obtains its eigenvalue and eigenvector which reflect the main diffusion direction in the given voxel (Pierpaoli and Basser, 1996). Fractional anisotropy (FA) is a metric which combines the eigenvalues in all three diffusion directions (Basser and Pierpaoli, 1996). FA value of zero depicts spherical, isotropic diffusion, whereas a maximal value one depicts a fully restricted, anisotropic diffusion.

In a DWI-MRI sequence, one of the crucial parameters is the *b*-value, which depicts the diffusion sensitivity and depends on the properties of the magnetic pulsed gradient (Stejskal and Tanner, 1965). A *b*-value of 0 means a T2-weighted MRI, in which only the mean diffusivity can be yielded for each voxel. To obtain the amount of three diffusion directions in each voxel, one has to grow the *b*-value (for example $b = 1000$). When the *b*-value gets larger, the specificity towards one diffusion direction increases. However, when the *b*-values gets large, the signal-to-noise ratio deteriorates (Burdette et al., 2001). In addition to the *b*-value, the amount and distribution of the diffusion gradients has to be determined when designing a DWI-sequence (Skare et al., 2000).

The data acquired from DWI-MRI can be utilized for the visualization of neuronal fiber tracts. Before performing the tractography, the images are preprocessed in various steps in order to minimize the effects of artifacts (Jones and Cercignani, 2010). Susceptibility-induced distortions can be corrected robustly, if the scanning sequence includes two reversed phase-encoding directions or if the diffusion directions are distributed on a sphere (Graham et al., 2016). Thereafter, the susceptibility-induced off-resonance field can be estimated (Andersson et al., 2003; Smith et al., 2004). Other sources of artifacts which need to be taken into account in the preprocessing pipeline, include motion and eddy current artifacts (Andersson and Sotiropoulos, 2016).

After the preprocessing steps, the fiber orientations can be estimated. There are several ways to model these orientations. For example, in the traditional diffusion tensor imaging (DTI) approach, a diffusion tensor is calculated for each voxel (Basser et al., 1994). This 3D ellipsoid can be characterized with three eigenvectors, which form a 3D ellipsoid. When one uses an approach, in which one tensor characterizes the properties of one voxel, the maximum diffusivity estimates the principal fiber orientation in the given voxel. This becomes a problem in the voxels which contain crossing fibers: for example, in a voxel in which the three eigenvalues are similar, the 3D profile of the tensor becomes a sphere, and it is impossible to tell in which ways the fibers are passing (Alexander et al., 2001).

Probabilistic tractography is one way of addressing the challenge of crossing fibers (Behrens et al., 2007). The idea is to model the uncertainty of the neuronal fibers in all voxels. This map can be utilized to create a probability map for example from a certain region of interest (ROI). Then, the map can be thresholded in such way that the nonspecific connections disappear. Thus, the probabilistic tractography estimates the *probability* of neuronal streamlines between two anatomical locations.

3. Aims of the thesis

The aims of the thesis were to study how temporal and spatial properties of tactile stimulation affect perception, and to investigate the functional organization of the PFC in the control of somatosensory processing. Tactile stimuli, perceptual and WM tasks, and evaluations of metacognitive ability were used. Moreover, novel combinations of brain imaging and brain stimulation were employed.

The aims more specifically:

1. To determine how the ability to discriminate between two tactile stimulus locations is influenced by temporal features of tactile stimulation (I).

2. To test whether the PFC contains segregated neuroanatomical substrates for the modulation of tactile temporal discrimination (II).

3. To assess whether the PFC contains segregated neuroanatomical substrates for metacognition of tactile WM (III).

4. Methods

4.1. Subjects (Studies I-III)

The subjects in all studies (I-III) were healthy, right-handed adults. Some of the subjects participated in more than one of the studies. The participants gave an informed consent and completed the safety-screening form before each study. Studies I and II were approved by the Ethical Committee of the Helsinki University Central Hospital. Study III was approved by the Ethical Committee of Aalto University. All studies took into account the code of ethics defined by the World Medical Association's Declaration of Helsinki.

Twelve subjects (seven females, age range 21-45 years) participated in study I, eight (three females, age range 23-31 years) in study II and 15 (seven females, age range 24-37 years) in study III. From study III, one subject was excluded due to misunderstood instructions.

4.2. Tactile stimulation and tasks

4.2.1. Electrotactile stimulation (Studies I and II)

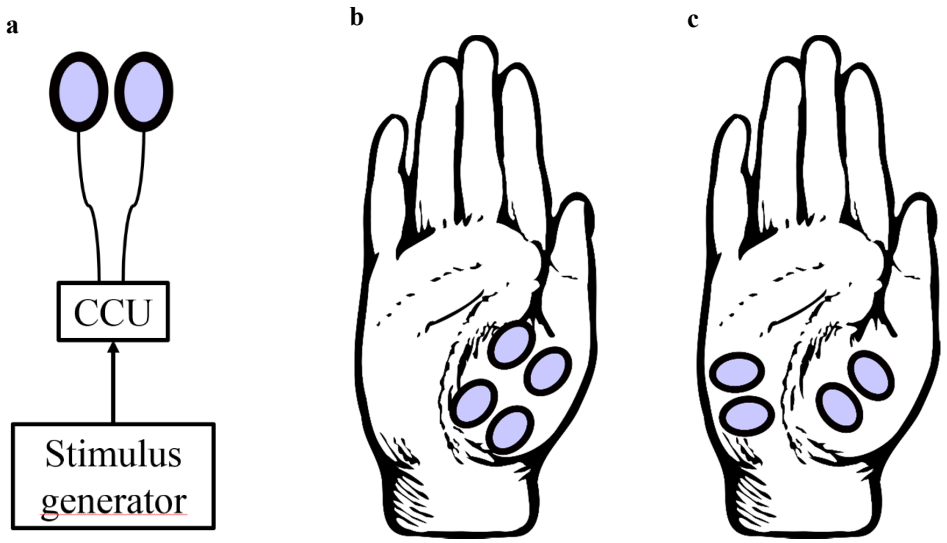

Figure 2: Electrotactile stimulation. (**a**) Illustration of the stimulator setup. (**b**) Electrode positioning in study I. (**c**) Electrode positioning in study II. The blue ellipses represent skin electrodes; CCU = Constant current unit.

In studies I and II, a PSIU6 constant current stimulator (Grass Instruments, Quincy, MA, USA) and Ag-AgCl skin electrodes (Ambu, Ballerup, Denmark) were used for delivering the electrotactile pulses (Fig. 2a). The size of the electrodes was 30 × 22 mm and the stimulation area of the electrodes was 18 mm^2. In both studies, a single tactile pulse had a duration of 0.2 ms. Before the main experiments of studies I and II, individual tactile threshold was assessed for each participant. The threshold was determined as an intensity that was felt in at least 90 % of the trials. In the main experiments of both study I and II, a tactile stimulus intensity twice as large as the threshold intensity was used. In study II, determination of the S1 representation site of the thenar was performed with threshold-level tactile stimuli.

In study I, two pairs of skin electrodes were attached to the thenar skin of the right hand (Fig. 2b). The distal pair of electrodes was 1 cm proximal to the first metacarpo-phalangeal joint, while the other pair of electrodes was 4 cm more proximally compared to the distal pair. The distance between the anode and cathode electrodes of the electrode pairs was 2.5 cm measured from the center of the electrode. For some subjects, the electrotactile stimuli elicited radiating sensations probably due to the stimulation of larger sensory axon bundles. In these cases, the placement of the electrodes was slightly changed and/or the intensity was reduced. In study II, the stimuli were delivered either to the thenar or hypothenar skin area of the right hand (Fig. 2c).

4.2.2. Mechanical stimulation (Study III)

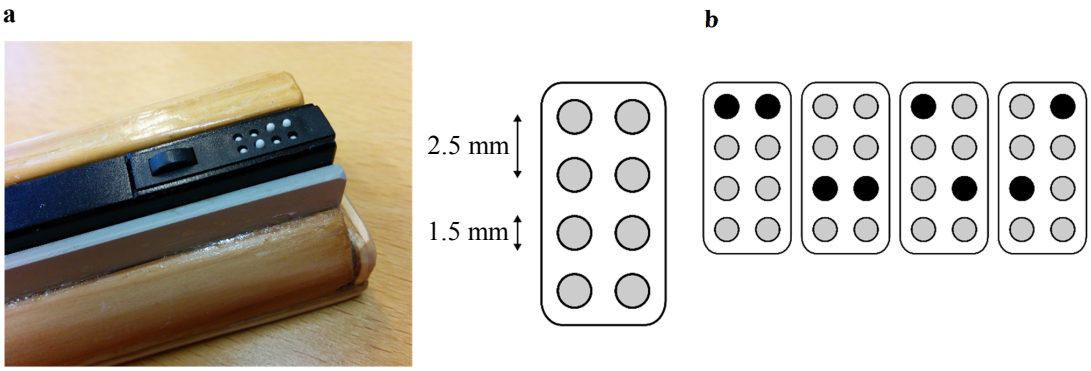

Figure 3: The Braille stimulator. (**a**) Image and illustration of the Braille stimulator. (**b**) Braille pin configurations used in the tactile WM tasks of study III.

In study III, a more natural, mechanotactile stimulus, instead of an electrotactile stimulus, was employed. The stimuli were delivered with a Braille stimulator (Metec AG, Stuttgart, Germany), originally designed for Braille reading (Fig. 3a).

Electrical stimuli activate somatosensory brain areas in a slightly different manner compared to naturalistic mechanical stimuli. Early somatosensory evoked magnetic fields (SEFs) from the S1 are smaller in amplitude and longer in latency to mechanical (air puffs) than to electrical stimuli (Forss et al., 1994; Rossini et al., 1996). Furthermore, mechanical, but not electrical, stimuli elicit off-responses also in the contralateral S1 (Onishi et al., 2010). However, the timing and control of stimulus intensity have posed a challenge when using mechanical stimuli (Jousmäki et al., 2007). In study III, these challenges were overcome with an in-house control system of the Braille stimulator that enabled precise and flexible control of the tactile stimuli.

Before the somatotopic blocking procedure in study III, a tactile threshold was assessed for each individual using different rising amplitudes of a single Braille pin. In the threshold measurement, eight blocks of six trials were presented. Each trial contained a Braille stimulus and a TMS pulse with an intensity of 50 % of the maximum stimulator output. TMS was delivered in the air (approximately 10 cm above the head) 20 ms after the tactile stimulus to make the test situation similar as in the somatotopic blocking procedure (see 4.3.). Each block included one sham stimulus (no tactile stimulus, only a TMS pulse). Different amplitudes of the pin were presented in random order. The amplitude which was perceived in 90 % of the trials was defined as the tactile threshold, and that

amplitude was used in the somatotopic blocking experiment. In the WM experiments of study III, clearly perceivable Braille stimuli were used.

4.2.3. Tactile tasks

4.2.3.1. Spatial perception tasks (Study I)

The first study of the thesis investigated whether the ability to discriminate the two pulses as spatially separate varies with ISI of the test stimulus pair. Additionally, it was tested whether the two-point discrimination ability varies with the length of the test pulse train. In the first experiment, the subjects received twin electrotactile pulses either to one skin location or to two different locations (Fig. 2b). The ISIs between the pulses varied (20, 40, 80, 120, 160 and 200 ms). In sham trials, the subjects received only one tactile pulse. By pressing the computer mouse buttons, the subjects responded whether they felt the stimuli in one or two skin locations.

In the second experiment, the influence of electrotactile pulse train length on spatial discrimination ability was investigated. The pulse trains consisted of either 3, 7 or 11 pulses (corresponding to train lengths of 40, 120 or 200 ms), which were delivered either to one skin location or simultaneously to two skin locations. Again, the task was to discriminate whether the trains were presented in one or two different locations. In both experiments, the subjects responded with a computer mouse as fast and as accurately as possible. During the tasks, the participants were instructed to visually fixate on a cross approximately at a 1 m distance.

4.2.3.2. Temporal perception task (Study II)

Study II investigated whether TMS to PFC locations that, according to tractography, had neural connections with the S1, influences the tactile temporal discrimination ability. An individual tactile temporal discrimination curve was determined for each participant before proceeding to the TMS experiment. The curve was performed so that the subjects were presented either a single tactile pulse or twin tactile pulses and they had to discriminate a single pulse from two pulses. On average, the subjects discriminated 90 % (minimum 80 %, maximum 100 %, standard deviation 10 %) of the twin pulses when the ISI was 90 ms, similarly as in an earlier study by Pastor et al. (2004).

In the TMS experiment, the individually determined ISIs, for which the temporal discrimination accuracy was 90 %, were used. During the experiment, the participants received single and twin electrotactile pulses either to the thenar or hypothenar skin (Fig. 2c). In each trial, the subject was instructed to respond as accurately and as fast as possible whether he/she felt one or two tactile stimuli. The responses were given verbally and by clicking a computer mouse. The subjects also gave a verbal confidence rating using a 3-level scale (3 = sure / high level of confidence, 2 = unsure / medium level of confidence, 1 = guess / low level of confidence).

4.2.3.3. Temporal and spatial working memory tasks (Study III)

While the first two studies of the thesis concentrated on tactile temporal and spatial perception, study III focused on tactile temporal and spatial WM, and in the metacognitive accuracy of tactile WM tasks. Based on our preliminary experiments performed with the Braille stimulator, a tactile WM task was designed in which the stimulus properties were similar across trials; only the instructions given for the participants changed between the spatial and the temporal WM task (Fig. 3).

Each trial consisted of two mechanical pin pair stimuli, which were delivered to the fingertip of the right index finger. The ISIs between the two consecutive pin-pairs were either same or different and varied between 120 and 430 ms. Also the spatial locations between the pin-pairs varied; the location of the second pin-pair stimulus was either same or different as the first one (Fig. 3b). The interval between the two pin-pairs (the delay period) was 2000-2300 ms and the TMS pulses were delivered during this delay period.

In the temporal WM task, the subjects were instructed to respond whether the ISIs of the two successive pin-pairs were the same or different. In the spatial WM task, they were asked to respond whether the spatial locations of the two pin-pairs were the same or different. The responses were given via a computer mouse after each trial (e.g. after two pin-pairs) and verbally. After each same/different response, the subjects evaluated verbally their confidence on a 3-level scale (3 = sure, 2 = unsure, 1 = guess). The responses were given as fast and as accurately as possible. During the tasks, the subjects were instructed to visually fixate on a small cross displayed in the center of the screen.

4.3. Navigated transcranial magnetic stimulation procedure (Studies II-III)

Table 1 summarizes the TMS parameters used in studies II and III. In study II an eXimia TMS Stimulator was used, which was operated with eXimia NBS navigation system (Nexstim Ltd., Helsinki, Finland). The TMS experiment was performed in Biomag Laboratory (Helsinki University Hospital). The TMS experiments of study III were conducted in Aalto TMS laboratory (Aalto NeuroImaging, Aalto University) employing a Magstim 200^2 stimulator unit (Magstim Co., Carmarthenshire, UK) and Visor2 navigation system (ANT Neuro, Enschede, Netherlands). 70 mm figure-of-eight coil and single, monophasic TMS pulses were used in all studies.

In both studies (II and III), the TMS intensity was determined using the rMT, which was measured from the abductor pollicis brevis (APB) muscle using an EMG device (Mega Electronics Ltd., Kuopio, Finland). The electric field produced by the TMS coil was oriented perpendicular to the postcentral sulcus, in an anterior direction. The location, which produced the largest EMG responses was determined as the M1 hotspot, and was selected as a target for the rMT measurement. The lowest TMS intensity which produced a peak-to-peak EMG response of ≥ 50 μV for $\geq 5/10$ stimuli was defined as the rMT. The mean rMTs (percentage of the maximal output of the stimulator) were: 54 % in study II and 42 % in study III. However, due to the two different TMS devices used in study II versus study III, those rMT values are not comparable with each other. In study II, the TMS was applied at 120 % of the rMT, whereas in study III the intensity was 110 % of the rMT.

Besides the stimulation intensity, also timing of the magnetic pulse is a crucial parameter in TMS studies. In the main experiment of study II, the TMS latency was determined as the time from the onset of the first tactile pulse to the onset of the TMS pulse. In the first part of study II, three different TMS latencies (0 ms, 20 ms and 50 ms) were used (Table 1). Of these three TMS latencies, the latency of 0 ms turned out to be most effective in the suppression of tactile temporal discrimination ability. Therefore, in two other parts of the study, only a TMS latency of 0 ms was used. In the main experiment of study III, the latency was determined as the time from the onset of the second tactile pulse (see section 4.2.3.). Based on a study by Hannula et al. (Hannula et al., 2010), a latency of 300 ms was used during the tactile WM tasks. This TMS latency of 300 ms fell upon the WM maintenance period.

In the main TMS experiments of study II and III, the TMS targets on the PFC were chosen according to individual tractography results (Fig. 4). The S1 representation areas of the right hand thenar (study II) or right index finger (study III) were used as tractography seed points. The individual locations of

the S1 representation areas were based on somatotopic blocking performed with TMS (see below). The end points of probabilistic fiber tracts in two different PFC areas (the MFG and the SFG) were defined as TMS targets in the tactile temporal discrimination experiment of study II and the tactile WM experiments of study III.

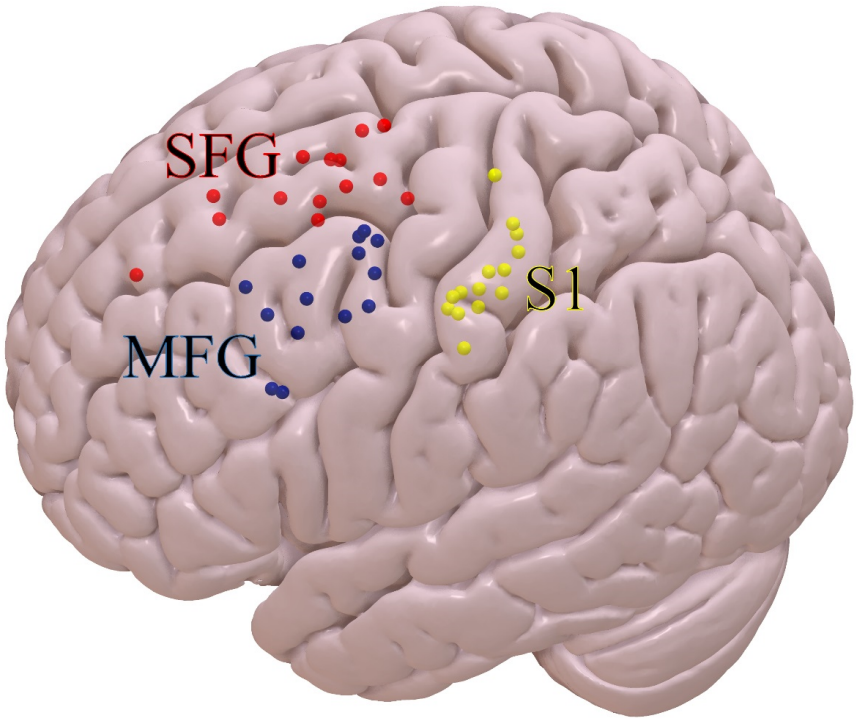

Figure 4: Visualization of TMS sites used in study III. The S1 representation site of each subjects' fingertip (yellow spheres) was determined with the somatotopic blocking procedure (Hannula et al., 2005). These blocking sites were used as seed points for probabilistic tractography between the S1 and the PFC. In study I, a similar procedure of TMS targeting was utilized. Red spheres = tractography ending points in the SFG; blue spheres = tractography ending points on the MFG. Rendering was performed with SurIce software (https://www.nitrc.org/projects/surfice/) using 'mni152_2009' template.

The control stimulation site, against which the behavioral effects are compared, is of great importance in TMS experiments. In the control condition of study II, TMS was applied with an intensity of 120 % of rMT with the coil approximately 5 cm above the head of the participant. When TMS pulses were applied above the head, the participants perceived the distracting clicking sound of the TMS coil but no sensation on the skin of the scalp. In order to produce also the distractive scalp sensation, a cortical control site was chosen in study III. The control site was defined as a midline target at the Pz electrode position of the standard 10-20 EEG electrode positioning system, and the electric field was directed caudally (Soutschek et al., 2013).

TMS parameters

Study number	TMS intensity (% of rMT)	TMS latency (ms)	TMS sites	Control site
II	120	0, 20, 50	S1, MFG, SFG	Coil in the air
III	110	20 (blocking experiment), 300 (WM tasks)	S1, MFG, SFG	Pz position

Table 1: TMS parameters. rMT = resting motor threshold, MFG = middle frontal gyrus, SFG = superior frontal gyrus, S1 = primary somatosensory cortex.

In addition to the temporal discrimination experiment in study II and the tactile WM experiments in study III, the individual somatosensory representation areas of the skin area where the tactile stimulus was applied, were determined with TMS using a somatotopic blocking procedure (Hannula et al., 2005). The aim was to functionally localize the individual somatosensory representation areas, which would serve as seed points for the probabilistic tractography. In the blocking procedure, single, navigated TMS pulses with an intensity of 120 % of rMT were delivered 20 ms after threshold-level tactile stimuli. The direction of the electric field was pointing posteriorly in relation to the central sulcus. The location in which the TMS succeeded to abolish the perception of the tactile stimulus was defined as the S1 hotspot.

4.4. Diffusion-weighted magnetic resonance imaging and tractography (Studies II and III)

In studies II and III, a T1-weighted 3D-MPRAGE structural MRI was acquired before the DWI scanning. In study, II the T1-weighted image consisted of 0.9 x 0.9 x 1.0 mm voxels, whereas in study III, the images had 1.0 mm isotropic voxels. MRI data (T1 and DWI) of both studies were acquired in Advanced Magnetic Imaging Centre (AMI Centre, Aalto University School of Science, Espoo, Finland).

In study II, the DWI scheme consisted of 60 diffusion-weighted images (b = 1000 s/mm^2) with non-collinear diffusion gradients. Four non-DW images (b = 0 s/mm^2) were collected. The imaging protocol consisted of the following parameters: single-shot diffusion-weighted echo-planar imaging (EPI) sequence, repetition time (TR) 10 000 ms, echo time (TE) 79 ms and 54 slices with a field-of-view (FOV) of 128 x 128 and 1.9 x 1.9 x 3.0 mm voxels. Before the DWI scanning, a manually adjusted high-order shim procedure was carried out. The imaging data was acquired twice, resulting in a set of 128 volumes.

In study III, the DWI procedure consisted of 64 non-collinear gradient orientations (b = 1000 s/mm^2), which were evenly distributed on a sphere. The scanning was performed with the following parameters: spin-echo EPI sequence, TR 9700 ms, TE 81 ms, bandwidth of 1436 Hz/px, echo spacing 0.78 ms, FOV 240 × 240 mm, 2.0 mm isotropic voxels, 65 contiguous axial slices and a GRAPPA factor of 2. Seven non-DWIs (b = 0 s/mm^2) with the anterior to posterior and six with the posterior to anterior phase-encoding direction were also collected. Before reconstruction, the raw k-space DWI data were filtered with a low-pass Hamming filter. Five subjects of study II participated also in study III; for these subjects, the previously collected DWI data of study II were utilized also in study III.

In study II, the processing of the diffusion-weighted data was performed with FSL pipeline. Motion correction and eddy currents correction were performed using FMRIB's diffusion toolbox and b0

volume as a reference image. The preparation for the probabilistic tractography was performed with BEDPOSTX tool of the FSL package (Behrens et al., 2003a; Behrens et al., 2003b). The brain extraction of the T1-weighted anatomical images was performed using BET and the diffusion-weighted volumes were coregistered to the T1-weighted images using FLIRT (Jenkinson et al., 2002).

In study III, the processing of DWI data was also performed with FSL package. As the *b*0 images were collected in two opposing phase-encoding directions, the susceptibility distortion correction was estimated using *topup* tool of FSL (Smith et al., 2004; Andersson et al., 2003) and the two images were combined into a single distortion-corrected image. Then, the acquired distortion correction field was applied to the diffusion-weighted images. Motion correction and eddy current correction were performed using EDDY tool (Andersson and Sotiropoulos, 2016). Similarly as in study II, the data was prepared for probabilistic tractography using BEDPOSTX.

After the processing of the diffusion-weighted image data, the connections between the S1 and the PFC were probed using PROBTRACKX tool of FSL (Behrens et al., 2003a). In both studies II and III, the seed mask for tractography was drawn individually for each subject according to the TMS somatosensory blocking coordinates (see section 4.3.). The coordinates of the somatotopic blocking site were transferred to the anatomical T1 image and the seed mask was registered to the diffusion space.

4.5. Analyses of behavioral data

4.5.1. Behavioral measures

In all three studies of the thesis, the subjects' response times were analyzed. In all tasks, the subjects were instructed to respond as fast and as accurately as possible. The mean response time of each subject was calculated in all task conditions.

In studies II and III, the participants were instructed to rate the confidence of each response on a 3-level scale (sure = 3, unsure = 2, guess = 1). In study II, the mean confidence in each condition was calculated for each subject. In study III, the responses were divided into "high confidence" and "low confidence" categories according to the subjective confidence ratings. The "sure" responses were defined as "high confidence", whereas unsure responses as "low confidence". The "guess" responses were omitted from the analyses due to the small amount of "guess" trials (only 87 "guess" trials in the entire data). The mean percentage of correct responses was calculated separately for both "high confidence" and "low confidence" responses similarly as in Lee et al. (2013).

4.5.2. Signal detection theory

Signal detection theory (SDT) is a framework that has been used in psychophysics since 1950's. The key concept of SDT is an observer who makes decisions under noisy and uncertain circumstances.

SDT has many applications in neuropsychology. Perhaps the simplest example is a task, in which a stimulus is presented and the subject is instructed whether he/she perceived the stimulus or not. In the basic SDT approach, the responses of the subject are divided into four categories: hit (stimulus is present, subject responds "yes"), miss (stimulus is present, subject responds "no"), correct rejection (stimulus is not present, subject responds "no") and false alarm (stimulus is not present, subject responds "yes").

After the categorization of responses, numerical metrics describing the discrimination abilities can be obtained. One can plot the values into relative operating characteristic (ROC) space, in which the *y*-

axis represents the relative amount of hits and *x*-axis the amount of false alarms (Swets, 1973). Plotting the values in the ROC space yields a curve. Area under the obtained curve [ROC(AUC)] depicts the subject's ability to discriminate whether the stimulus was presented or not; an AUC value of 0.5 represents a chance level, whereas the value of 1.0 represents a perfect discrimination ability. Another measure of the subject's sensitivity is *d'*, which is computed as a distance of the curve from the chance level line.

Sometimes the subject tends to respond more frequently "yes" than "no", regardless of whether the stimulus was present or not. The tendency of responding either way can be characterized with a value called response bias. Response bias is independent from ROC(AUC) and *d'*.

The aforementioned way of calculating the ROC curve is referred to as type 1 ROC. Another perspective of SDT is taking into account the subject's confidence ratings, namely the type 2 ROC. In the type 2 ROC approach, the responses of the subject are classified into the following categories: hit (correct type 1 response, high confidence), miss (correct type 1 response, low confidence), correct rejection (incorrect type 1 response, low confidence) and false alarm (incorrect type 1 response, high confidence). The type 2 ROC(AUC) is affected by the type 1 performance, which makes it difficult to use for the assessment of metacognitive performance (Fleming and Lau, 2014).

A recently developed, SDT-based measure called meta-*d'* takes another angle of approach for the measurement of metacognition and exploits the fact that there is a mathematical link between the type 2 and type 1 performance (Maniscalco and Lau, 2012). In this method, the observed type 2 ROC is expressed in type 1 terms. In other words, meta-*d'* stands for a value of *d'* which a metacognitively perfect observer would have needed to produce for yielding an observed type 2 ROC. The elegance of the method is in the possibility of comparing the computed meta-*d'* with the empirical *d'*; since both are expressed in the same units, they can either be subtracted (meta-*d'* – *d'*) or divided (meta-*d'* / *d'*) with each other. The meta-*d'* metric is independent from type 2 response bias and type 1 performance (Barrett et al., 2013), which makes it a powerful tool for assessing metacognitive accuracy.

4.5.3. Statistical tests

The individual ROC(AUC) –values, response times and confidence ratings in study I were analyzed with 1- and 2-way repeated measures analyses of variance (rmANOVA). For post hoc testing, *t* tests with Bonferroni multiple comparisons correction was applied. In study II, ROC(AUC) –values, response times and confidence ratings of the first two experiments were analyzed with 2-way rmANOVAs followed by Tukey's post hoc tests. The data of the third experiment (TMS of the MFG, the SFG or sham stimulation) were analyzed with a 1-way rmANOVA, followed by post hoc Tukey's tests. Besides the bootstrap analyses (see the section below), 2-way rmANOVAs were used in study III. The rmANOVAs were applied for analyses of the response times, the WM performance in different levels of confidence, the type 1 response bias and the type 2 response bias. For the post hoc testing, Tukey's multiple comparison tests were used. In all three studies of thesis, a *P*-value of < 0.05 was considered to represent a statistically significant difference.

4.5.4. Bootstrap analyses (Study III)

Bootstrapping is a statistical resampling method, which can be used to estimate for example confidence intervals (CIs) (Mooney et al., 1993), (Fig. 5). This method was used in study III in the following manner. First, the behavioral response data of all subjects were pooled together and divided into subsets according to each WM task and TMS site. Each subset contained *n* trials. Thereafter, a

bootstrap sample of *n* trials was drawn with replacement from the pooled subset of data. For this bootstrap sample, the meta-*d'* and *d'* were calculated (value *X* in Fig. 5). The bootstrap sampling and calculation of meta-*d'* and *d'* was repeated *B* times, here specifically 100 000 times. Values of these 100 000 samples formed distributions for which 95 % CIs were calculated, and the CIs were used for statistical comparisons of each TMS site within both WM tasks.

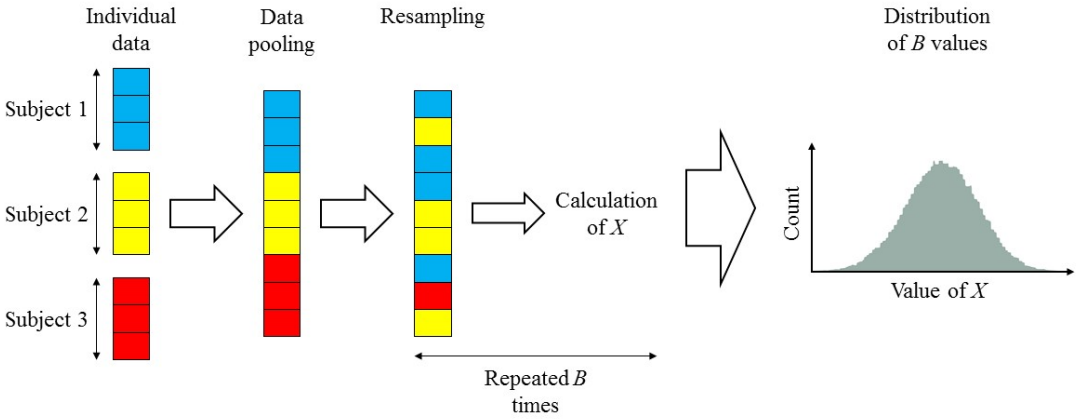

Figure 5: Example of a bootstrap sampling procedure. First, the data of each individual is pooled together. Then, a bootstrap sample is randomly resampled with replacement. Calculation of the wanted value (*X*) is performed for the bootstrap sample. The resampling and calculation steps are repeated *B* times, which produces a distribution of *B* values. From the obtained distribution, for example standard deviation can be calculated and used for further statistical comparisons.

5. Results and discussion

5.1. Study I

In study I of the thesis, the aim was to examine how temporal aspects of tactile stimulation affect spatial discrimination ability. One of the motivations was to find optimal parameters for future TMS experiments, in which the spatial discrimination ability could be further studied. Two-point discrimination of electrotactile stimulation was used as an indicator of spatial discrimination ability.

The first part of study I examined, how the ISI between two consecutive tactile stimuli influence the spatial discrimination ability. With a short 20 ms ISI, the subjects could not perceive two stimuli as spatially separate [95 % CI of the ROC(AUC) overlapped with value 0.5 (range 0.478–0.652)]. The two-point discrimination ability varied significantly when the ISI was prolonged ($F_{5,7} = 10.2$, $P < 0.001$). Post hoc comparisons showed that the spatial discrimination ability was improved when the ISI was increased from 20 ms to 120 ms or longer (120, 160 or 200 ms compared to 20 ms: $P < 0.005$). Prolongation of the ISI had no statistically significant influence on response times ($F_{5,7} = 2.1$, $P = 0.059$).

The next question was, how the length of an electrotactile stimulus train influences the spatial discrimination ability. The results showed that prolongation of the stimulus train length had an influence on spatial discrimination ability, as shown by the ROC(AUC) values ($F_{2,11} = 4.8$, $P = 0.018$). Post hoc testing indicated that the two-point discrimination ability was improved when the stimulus train length was prolonged from three to 11 pulses ($P < 0.05$). Moreover, the response times varied significantly with the stimulus train length ($F_{2,11} = 3.8$, $P = 0.038$), which was in line with the ROC(AUC) results.

In conclusion, study I showed that the two-point discrimination of electrotactile stimuli is affected by temporal properties of the stimulation. Moreover, the study revealed that with electrotactile stimuli, even when the distance between the two electrode pairs is 4 cm, it is not always trivial for a subject to discriminate the stimuli as spatially separate. This possibly relates to the nature of the electrotactile stimulation; electrotactile stimulation activates the peripheral sensory nerves in different way as mechanical stimulation (Krarup and Trojaborg, 1994).

5.2. Study II

The second study of the thesis examined whether the neural tracts between the PFC and the S1 modulate tactile temporal discrimination. A similar approach as in (Hannula et al., 2005) was used to determine the individual S1 representation area of each subject's thenar skin. Using DWI-based probabilistic tractography, two distinct neural connections were detected between this functionally determined S1 area and the PFC: the S1-MFG –link and the S1-SFG –link. As expected, the locations in the MFG and the SFG varied between subjects motivating the use of tractography-guided TMS.

In the first part of the study, temporal properties of TMS were studied. TMS was targeted to the MFG during the temporal discrimination task, and three TMS delays (0, 20 and 50 ms from the tactile test pulse) were investigated. Tractography-guided TMS applied to the MFG-S1 –link impaired tactile temporal discrimination ability when ROC(AUC) was compared to sham stimulation (main effect of TMS: $F_{1,6} = 9.94$, $P = 0.02$). The impairment in the discrimination ability occurred in a restricted time window, as shown by the main effect of TMS delay ($F_{2,12} = 5.89$, $P = 0.017$). Post hoc Tukey's test showed that, compared to sham stimulation, the reduction in the temporal discrimination ability was most pronounced when the TMS was applied simultaneously with the electrotactile stimulus ($P < 0.05$). Post hoc comparisons of other TMS delays (20 or 50 ms) against sham stimulation were non-significant, indicating a temporally specific effect of TMS. Analysis of the response times showed no

significant difference between TMS of the MFG and sham stimulation (main effect of TMS: $F_{1,6}$ = 4.42) nor a significant difference between different TMS delays (main effect of TMS delay: $F_{2,12}$ = 1.5, P = 0.244). Analysis of confidence ratings revealed that TMS of the MFG reduced the average confidence ratings when compared to sham stimulation (main effect of TMS: $F_{1,6}$ = 13.15, P = 0.011), whereas TMS delay did not affect the confidence ratings (main effect of TMS delay: $F_{2,12}$ = 0.6, P = 0.56).

Next, the location of the cutaneous test stimulus was changed from the right thenar to hypothenar, and TMS was applied to the previously determined MFG area. Similarly as in the first experiment, TMS of the MFG suppressed the tactile temporal discrimination ability when compared to sham stimulation, as was shown by the main effect of TMS ($F_{1,7}$ = 13.1, P = 0.0085). Temporal discrimination ability varied with the cutaneous test site (main effect of cutaneous test site: $F_{1,7}$ = 9.14, P = 0.019). Importantly, there was a significant interaction of cutaneous test site and TMS condition ($F_{1,7}$ = 5.83, P = 0.047). Post hoc testing showed that TMS of the MFG impaired the temporal discrimination ability only when the cutaneous stimulation was applied to the thenar (P < 0.01), but not to the hypothenar area. Changing the cutaneous test site from thenar to hypothenar skin resulted in significant difference in the temporal discrimination ability (P < 0.01) indicating that the effect of TMS was dependent on the stimulated skin area. Analyses of confidence ratings and response times showed no significant differences between different cutaneous test sites or between different TMS conditions (the MFG or sham stimulation). In conclusion, the results of the second experiment suggested that the PFC could be somatotopically organized.

Finally, spatial specificity of TMS was examined. For this purpose, TMS was applied on a different PFC subarea that has neural connections with the S1 (the SFG), and the temporal discrimination ability was again measured. The suppressive effect of TMS on temporal discrimination ability was dependent on the stimulated PFC location (1-way ANOVA: $F_{2,10}$ = 6.52, P = 0.015). This suggested that different subregions of the PFC may have specific modulatory functions in the regulation of tactile sensations. Post hoc testing showed significant differences between the MFG and the SFG (P < 0.05) stimulation and between the MFG and sham stimulation (P < 0.05), while the difference between the SFG and sham stimulation was non-significant. Thus, TMS of the MFG, but not that of the SFG, selectively impaired the tactile temporal discrimination ability. In line with these ROC(AUC) results, the response times of the third experiment varied significantly with the TMS site ($F_{2,10}$ = 4.46, P = 0.041), and the post hoc test showed a significant difference between TMS of the MFG and the SFG (P < 0.05). 1-way ANOVA of the confidence ratings showed no significant differences between the MFG, the SFG and sham stimulation ($F_{2,10}$ = 0.4, P = 0.68). Altogether the results of the third experiment indicated that the PFC may contain functionally specialized subareas.

Taken together, the results of study II showed that the PFC modulates tactile temporal discrimination in a highly segregated fashion. First, the temporal properties of TMS-induced effect were specific; temporal discrimination ability was reduced by TMS of the MFG only at a TMS delay of 0 ms. Second, the reduction of temporal discrimination ability was specific to TMS stimulation site on the PFC; when TMS pulses were applied to the SFG, temporal discrimination did not differ significantly from that of the sham stimulation condition.

Analyses of confidence ratings showed significant differences in the first experiment of study II, in which TMS of the MFG applied with different delays was compared with sham stimulation. Compared to sham stimulation, TMS of the MFG reduced the confidence only when the TMS delay was 20 or 50 ms, but not when the delay was 0 ms. It is worth noticing that in the second and third experiment of study II, only a TMS delay of 0 ms was tested. Thus, one might speculate that with longer TMS delays, stimulation of the SFG could affect the confidence ratings of temporal discrimination, but this remains to be investigated in the future. On the other hand, the finding that

TMS of the SFG did not affect the overall the confidence level is in line with the results of study III, according to which TMS of the SFG affected only the matching of confidence with task accuracy.

5.3. Study III

The PFC has been shown to be involved in many cognitive functions, including WM and attention. Recently, it has also been suggested to have a critical role in metacognition (Fleming and Dolan, 2012), an ability to evaluate one's own cognitive processes (Nelson and Narens, 1990). The aim of study III was to investigate the functional architecture of somatosensory metacognition using navigated, single-pulse TMS during tactile WM tasks. The subjects performed tactile temporal and spatial WM tasks and gave a confidence rating after each response. Navigated TMS was applied during the WM maintenance period to two distinct, tractography-informed prefrontal targets that had connections with the S1 cortex: the SFG and the MFG.

For the pooled behavioral data, the meta-$d' - d'$ for each task- and stimulation site-combination were calculated with a bootstrap analysis procedure. For the statistical analysis, the 95 % CIs of the bootstrap distributions were compared to each other. The analysis of the bootstrapped 95 % CIs showed that TMS applied to the SFG enhanced the metacognitive accuracy in the temporal WM task when compared to the effect of TMS of the MFG or control site (SFG: −0.30 to 0.74; MFG: −1.56 to −0.47; Control: −1.67 to −0.50). The CIs of the MFG and control site results overlapped, which indicated that stimulation of the MFG did not have a significant effect on metacognitive accuracy in the temporal WM task. Moreover, the 95 % CI of the SFG-induced bootstrap distribution overlapped with zero, indicating an optimal metacognitive performance.

In the tactile spatial WM task, the 95 % CIs of bootstrap distributions in all three TMS conditions (the SFG, the MFG and control site) overlapped (SFG: −1.20 to −0.19; MFG: −0.70 to 0.30; Control: −1.17 to −0.09). Thus, in the spatial WM task, TMS of neither the MFG nor of the SFG affected the metacognitive accuracy.

The bootstrap distributions across the two WM tasks were also computed for each stimulation site [(bootstrap distribution of spatial WM task) – (bootstrap distribution of temporal WM task)]. In the control site condition, the resulting 95 % CI (−0.35 to 1.28) overlapped with zero, showing that the baseline metacognitive accuracy did not differ between the tasks. The 95 % CI of the bootstrap distribution in the MFG condition (0.08 to 1.51) suggested that the metacognitive performance was better in the spatial compared to the temporal WM task. In line with the other bootstrap analyses, the 95 % CI of the bootstrap distribution in the SFG condition (−1.60 to −0.21) suggested a better metacognitive accuracy in the temporal compared to the spatial WM task.

Additional analyses of the metacognitive accuracy were also performed, namely the bootstrapped, response-specific meta-$d' - d'$ (Maniscalco and Lau, 2014) and the HMeta-d (Fleming, 2017). The response-specific bootstrap analyses showed that the enhancement of metacognitive accuracy by TMS of the SFG was manifested especially when the subjects responded "same". The calculations performed with HMeta-d methodology provided similar results as the ones shown above: metacognitive accuracy of the temporal WM task was improved when TMS was applied to the SFG.

After the bootstrap analyses, the responses of each subject were sorted in accordance with the confidence ratings. Percentages of correct responses were analyzed in both WM tasks separately. In the temporal WM task, the 2-way rmANOVA revealed an association of confidence with the WM performance ($F_{1,13} = 55.10$, $P < 0.0001$). Thus, the WM performance was better in the trials which were rated as "high confidence", as opposed to the trials rated as "low confidence". The main effect of stimulation site was not statistically significant ($F_{2,26} = 2.49$, $P = 0.10$). The interaction of confidence and stimulation site in the temporal WM task was significant ($F_{2,26} = 4.80$, $P = 0.017$),

suggesting a confidence-specific modulatory effect of TMS on the WM performance. Post hoc comparisons revealed that TMS of the SFG influenced the ability of the subjects to rate incorrectly performed trials as low confidence trials more often than when TMS was applied to the control (P = 0.0044) or the MFG sites (P = 0.012). In the spatial WM task, the percentage of correct responses was associated with confidence ($F_{1,13}$ = 26.51, P = 0.0002), but the main effect of stimulation site ($F_{2,26}$ = 0.29, P = 0.75) and the interaction of confidence and stimulation site ($F_{2,26}$ = 1.16, P = 0.33) were non-significant.

The analysis of response times showed that confidence was associated with response times in both the temporal (2-way rmANOVA, confidence factor: $F_{1,13}$ = 49.70, P < 0.0001) and spatial ($F_{1,13}$ = 58.14, P < 0.0001) WM tasks. Thus, the subjects responded faster in the trials which were rated as "high confidence". In both tasks, main effect of the stimulation site (temporal WM task: $F_{2,26}$ = 2.33, P = 0.12; spatial WM task: $F_{2,26}$ = 2.47, P = 0.10), and interaction of stimulation site and confidence (temporal WM task: $F_{2,26}$ = 1.42, P = 0.26; spatial WM task: $F_{2,26}$ = 1.98, P = 0.16) were non-significant. These non-significant results showed that TMS did not affect the response times in either the temporal or spatial WM task.

Taken together, the results of study III showed that single-pulse TMS of a tractography-informed site on the SFG enhanced metacognitive accuracy in the tactile temporal WM task. The improvement in introspection was manifested as lower confidence in the incorrectly performed trials. By contrast, in the spatial WM task in which the tactile stimulus parameters were identical to temporal WM task, TMS of neither the MFG nor the SFG affected the metacognitive accuracy. Interestingly, a recent MEG study by Whitmarsh et al. discovered a negative correlation between the alpha power in the left superior frontal area and metacognitive evaluation of somatosensory attention (Whitmarsh et al., 2017). One possible explanation for the finding of Study III is that TMS to the SFG may have modulated the alpha band oscillations, but this remains to be investigated in the future.

6. General discussion

The main aim of this thesis was to explore the functional organization of the PFC in the control of tactile WM and metacognition by utilizing a combination of brain imaging and brain stimulation methods. The cognitive functions were studied with different kinds of tactile tasks. Moreover, the processing of the temporal and spatial aspects of tactile stimuli were studied. The initial motivation for the methodology used in the thesis arose from earlier findings which have suggested that tractography-guided TMS can be successfully used for studying the PFC control of the S1 (Hannula et al., 2010). Below I will first summarize and discuss the findings of each study of the thesis and provide general comments concerning the results presented in the thesis. The methodology that was used in this thesis will be commented in section 6.2.

6.1. Control mechanisms of perception, working memory and metacognition

In order to be able to study the temporal and spatial aspects of tactile processing, first one needs to know how these two components interact. Thus, in the first study of the thesis, the spatial discrimination ability of electrotactile stimulation was investigated as a function of temporal aspects of stimulation. Increasing the ISI of two consecutive tactile pulses resulted in improved two-point discrimination ability. The pulses were perceived as spatially separate when the ISI was over 120 ms. Surround inhibition in tactile relay neurons occurs in a similar time frame (< 100 ms; Jänig et al. (1977); Jänig et al. (1979)). It may be speculated that surround inhibition reduced perception and discrimination of the two cutaneous test stimuli when they were simultaneously delivered to the adjacent sites, while with prolongation of the ISI between the two tactile test stimuli the suppressive effect of surround inhibition disappeared leading to improved spatial resolution. Another finding of study I was that the prolongation of the electrotactile pulse train from 3 to 11 pulses (corresponding to 40-200 ms) resulted in improved two-point discrimination by increasing the magnitude of sensory perception. This result could be explained by supramedullary mechanisms, since at the dorsal column nucleus level, the duration of the vibrotactile stimulus train did not affect the neuronal response thresholds (Pertovaara et al., 1986). In general, study I showed that the timing of tactile stimulation is critical when tactile spatial processing is being studied.

While study I focused on the "lower" level – presumably thalamic and medullary – control mechanisms of tactile perception, study II delved into the cortical processes. The role of the PFC in tactile temporal discrimination was examined with navigated, single-pulse TMS. The cortical targets for TMS were chosen based on individualized neural tractography between the S1 and two PFC areas of interest (the SFG and the MFG). TMS of the MFG impaired tactile temporal discrimination ability when tactile stimulation was applied to the hand thenar but not hypothenar area. Additionally, TMS of the SFG did not affect the tactile temporal discrimination ability. In conclusion, the results of study II implied that the PFC could possess functionally and somatotopically differentiated subareas for the modulation of tactile temporal perception.

The third study focused on "higher" levels of cognition, namely the WM and metacognition. A similar TMS methodology was employed as in study II, i.e. on single-pulse TMS and tractography-based targets on the PFC (the MFG and the SFG). TMS of the SFG enhanced the metacognitive accuracy of tactile temporal WM, but not that of tactile spatial WM. The enhancement of metacognitive accuracy was manifested as the improved ability of the subjects to match the incorrectly performed trials with lower confidence. TMS of neither the MFG nor the SFG, on the other hand, affected the metacognitive accuracy of tactile spatial WM. The WM performance (overall percentage of correct answers) of neither the temporal nor spatial WM was affected by TMS.

The functional organization of WM in the PFC has been suggested to be based on the involvement of different cognitive processes of WM (Petrides, 2005). Another theory suggests that the PFC is organized based on the type of stimuli held in WM (Goldman-Rakic, 1995). Additionally, different temporal stages of the perceptual decision making process have been suggested to be represented in the PFC along the rostrocaudal axis (Rahnev et al., 2016). The findings of this thesis suggest that the dorsal parts of the dorsolateral PFC (the SFG) fine-tune the introspective processes of WM and the lateral parts (the MFG) serve the perceptual decisions in which WM is less involved.

The underlying mechanism that caused the impairment in temporal discrimination ability, a strictly perceptual task, by TMS of the MFG-S1 link in study II, remains to be investigated. TMS of this link has earlier been shown to facilitate temporal WM which was suggested to be due to facilitation of the top-down mechanism that suppresses distractive signals in S1 (Hannula et al., 2010). Effect of TMS is thus dependent on the type of ongoing neural processing. In study II, TMS of the MFG-S1 link during a perceptual discrimination task may have slightly modified tactile perceptions via the top-down sensory gating mechanisms (Yamaguchi and Knight, 1990; Chao and Knight, 1995) resulting in impaired temporal discrimination. The finding that TMS of the SFG did not affect the temporal discrimination ability, suggests that stimulation of the MFG affected specifically the discrimination, and the effect did not arise merely due to a distractive sensation induced by the TMS pulse. As the lateral PFC is highly connected with several other brain areas (Rojkova et al., 2016) and is involved in cognitive control (Miller and Cohen, 2001), other modulatory cognitive effects of TMS cannot be completely ruled out. However, if a general modulatory effect of TMS, such as modulation of attention, were present, the effects of TMS should not have varied with the location of cutaneous test site. In study II, TMS of the MFG did not influence the temporal discrimination ability when the cutaneous test site was changed to the hypothenar instead of thenar skin area.

During the WM maintenance period, the PFC has been suggested to interact with the primary sensory areas by several oscillatory rhythms such as theta, alpha and gamma (Ku et al., 2015a). Moreover, single-pulse TMS has been shown to induce widely distributed changes in cortical oscillations (Rosanova et al., 2009). Therefore, the results of studies II and III might be at least partly explained by the influence of TMS on cortical rhythms. However, this hypothesis remains to be studied.

6.2. Methodological advantages and limitations

Perhaps the greatest advantage of TMS is that it provides a relatively straightforward way to interpret the causal relations between the studied cognitive function and the stimulated brain area. In this thesis, navigated, tractography-guided TMS was used to study tactile perception, WM and metacognition. The interindividual functional variability which is large in the PFC was taken into account by using tractography for the targeting of TMS. Online navigation was employed to ensure the spatial accuracy of the TMS pulses. Moreover, the use of time-locked, online single-pulses instead of offline repetitive TMS enabled temporally precise TMS delivery.

In study III, the Braille stimulator provided delivery of natural, mechanical stimulation. In the spatial and temporal WM tasks, the Braille stimuli were identical; only the instructions for the subjects were different in the tasks. Thus, there were no stimulus-related confounds that could result in differences of the performance between the two tasks.

Assuming the Gaussian distribution and using parametric statistical analyses of response times may sometimes be problematic due to the positively skewed distributions that violate the normality assumption (Leth-Steensen et al., 2000; Ulrich and Miller, 1994). Therefore, also other behavioral parameters such as the ROC curve, percentage of correct responses and confidence ratings were used in the studies of the thesis. The ROC(AUC) that was used as an indicator of performance in studies I

and II, is independent of subject's response criterion, and thus, reliably reflects the sensory discriminability (Swets, 1973). Meta-*d'* which was exploited to determine metacognitive accuracy in study III has been shown to be independent of type 2 response bias and type 1 performance (Maniscalco and Lau, 2014).

The studies of this thesis have several limitations. Especially in study I and II, the number of test subjects was relatively low. The first experiment of study II (the effect of different TMS delays on the suppression of tactile temporal discrimination) involved 7 subjects. The second part of the study (spatial properties of the effect of TMS) had 8 subjects and the third part (subregions of the PFC) only 6 subjects. However, the data of relatively few subjects produced fairly robust results. Another limitation of study II was that for the hypothenar skin site, another tactile temporal discrimination curve was not assessed before proceeding to the TMS experiment. Thus, one could speculate that the result of the experiment might be influenced by different psychophysical properties of hypothenar and thenar skin stimulation. Although not probable, this possibility should be explicitly addressed in the future.

In study III, a data pooling approach was used for the statistical analyses of metacognitive accuracy. Although the bootstrap analysis was reasonable given the low number of trials, the analysis of individual subjects would have been the preferable choice. The analysis of individual subjects could have yielded unstable estimates of meta-*d'* (Barrett et al., 2013) so in the given experimental conditions, the bootstrap sampling was a rational approach. In TMS studies in which the task requires high attentional focus of the participants (such as a WM task), the length of the experiment and the number of TMS pulses have to be within reasonable limits. In order to make sure that our results were not affected by the bootstrap procedure, the analyses of metacognitive accuracy were supplemented with a recently developed, hierarchical Bayesian model of meta-*d'* (Fleming, 2017) and with response-specific meta-*d'* (Maniscalco and Lau, 2014).

In study II and III, probabilistic tractography was used to determine the anatomical connections between the S1 and the PFC. Deterministic tractography approaches have been stated to outperform probabilistic ones in the long-range fiber connections, while the probabilistic approaches seem to operate better in regions with many crossing fibers (Khalsa et al., 2014). The FSL's ball-and-stick model that was implemented in studies II and III, has been criticized for the asymmetry of the probabilistic maps: it is possible that placing the seed region to the end point of the tracts produces a different tractography result than when placing a seed to the original starting point (Wandell, 2016). Other general challenges which apply to all current brain tractography techniques are the limited angular resolution, vast number of false connections and poor spatial resolution (Jeurissen et al., 2017). Moreover, in the studies of the present thesis, the size of the tractography seed regions was somewhat arbitrary. Thus, it would be reasonable to re-validate the connections found in studies II and III with other tractography techniques.

7. Conclusion

Study I of the thesis demonstrated that the ability to discriminate two tactile stimuli as spatially distinct is influenced by temporal features of stimulation. Study II revealed that TMS of a PFC target (the MFG) that had neural connections with the S1 modulated tactile temporal discrimination ability. Another prefrontal area that also had connections to the S1 (the SFG) did not affect the temporal discrimination ability. Study III exploited a similar kind of methodology as in study II for targeting TMS to the MFG and the SFG. The study showed that TMS of a location in the SFG that was connected to the S1 improved introspective performance of tactile temporal WM. The enhancement of metacognition was manifested as improved awareness of subjects' own performance level in incorrectly performed trials.

8. Suggestions for future work

In study III, TMS of the SFG location that according to tractography had neural connections with the S1, enhanced the metacognitive accuracy of tactile temporal WM task. TMS of another tractography-informed prefrontal area, the MFG, did not affect the metacognitive accuracy. Very few earlier studies have investigated the neurobiological substrates of tactile metacognition (Whitmarsh et al., 2014; Whitmarsh et al., 2017). In these studies, the meta-*d'* metric was not utilized for the assessment of metacognitive accuracy. Thus, more behavioral and neuroimaging studies on tactile metacognition are needed. The observation of study III, according to which the metacognitive accuracy of tactile WM can be enhanced with single-pulse TMS, could also have clinical relevance. It would be tempting to test whether the metacognitive accuracy of neuropsychiatric patient populations (David et al., 2012) could be improved with navigated TMS. A recent study by Hauser et al. (2017) showed that the metacognitive accuracy of visual perception can be enhanced with pharmacological blocking of beta adrenoceptors. Thus, perhaps a combination of pharmacological intervention and TMS could be the most efficient way of enhancing metacognitive accuracy.

In the studies of this thesis, only tactile stimuli were used. It remains to be investigated whether the findings presented here can be generalized to auditory and visual modalities. The temporal and spatial WM tasks used in study III could be easily translated into a visual version, and the neural processes associated with these two types of visual tasks could be studied with TMS. Additionally, the prefrontal control mechanisms of cross-modal stimuli (for example tactile-tactile, tactile-auditory or tactile-visual) could be investigated with navigated TMS.

TMS-EEG has already shown to be a useful diagnostic tool in consciousness disorders (Casarotto et al., 2016). For psychiatric illnesses, it has proven to be difficult to find clinically useful biomarkers by using solely brain imaging (fMRI or DWI) without TMS (Woo et al., 2017; Kambeitz et al., 2017). A combination of navigated TMS and DWI may help in developing more specific and sensitive diagnostic tools for neuropsychiatric conditions. For example, patients suffering from schizophrenia have been shown to have disturbed metacognition (David et al., 2012) and auditory temporal discrimination (Todd et al., 2003). Perhaps these kind of functional disturbances could be tested in vivo with personalized, tractography-informed TMS.

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